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For a prospective study of lead exposure, iron status, and infant development, we recruited infants living in a smelter town and a non-lead-exposed town in Kosovo, Yugoslavia. Among 392 infants assessed at age 2 years, the mean Mental Development Index (MDI), Bayley Scales of Infant Development, was 105.2. At age 2 years, geometric mean blood lead concentrations were 35.5 and 8.4 μg/dl, respectively, among infants from the exposed and nonexposed towns. After controlling for variables associated with MDI, we found significant independent associations for both blood lead and hemoglobin concentrations. For example, a rise in blood lead concentration at age 2 years from 10 to 30 μg/dl was associated with an estimated 2.5 point decrement in MDI ($p = 0.03$); statistically nonsignificant decrements were associated with blood lead levels measured at birth and at 6, 12, and 18 months of age. A decrease in hemoglobin concentration at 18 months of age from 12 to 10 gm/dl was associated with an estimated 3.4 point decrement in MDI ($p = 0.02$); the latter association was present in both towns, suggesting that it was due to iron deficiency anemia independent of lead exposure. The findings suggest that the brain is vulnerable to the effects of both lead exposure and anemia before 2 years of age. On a global basis, the developmental consequences of anemia may exceed those of lead exposure. (J PEDIATR 1992;121:695-703)

Retrospective and cross-sectional studies have reported that children with an increased lead burden performed less well than their peers in both standardized intelligence tests and academic functioning.[1-5] Numerous reviews (e.g., Yule and Rutter[6]) have indicated that interpretation of these observations is hindered by the inherent limitations of the study designs: lack of appropriate comparison groups, imprecise

BPb	Blood lead
EP	Erythrocyte protoporphyrin
HOME	Home Observation for Measurement of the Environment
MDI	Mental Development Index

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Table I. Selection of infants for the prospective study

	K. Mitrovica (n = 418)*			Pristina (n = 566)†	
	Group 1	Group 2	Group 3	Group 4	Group 5
Cord BPb criteria (μg/dl)	<15	15-20	>20	NA	NA
Eligible	78	106	234	NA	NA
Asked to participate	78	99	217	91	221
Consented and seen at 6, 12, 18, and/or 24 mo	62	75	161	64	179
Seen at 24 mo (reported herein)	36	57	115	49	135

NA, Not applicable.
*In K. Mitrovica, there were 442 infants with complete follow-up during pregnancy; however, 24 infants were excluded according to the selection and exclusion criteria described in the Methods section. Therefore only 418 infants were eligible for the study.
†Number of infants with complete follow-up during pregnancy.

measurement of exposure, use of crude outcome measures, lack of adjustment for potential confounders, and problems of statistical analysis.

Four recent prospective studies[7-15] measured cord blood lead concentration, infant BPb concentration, and early development for an extended period. Although findings on the magnitude and timing of associations are inconsistent among the studies, the emerging consensus is that low-level lead exposure is associated with some degree of developmental deficit. The possibility exists, however, that some of the observed effects attributed to lead exposure may be due to concomitant iron deficiency, the most common cause of anemia in the world.[16, 17] The clinical effects of iron deficiency are not limited to anemia but include, among others, possible decrements in the intelligence of children. Iron deficiency, particularly in association with anemia, has been associated with lower scores on the Bayley Scales of Infant Development, on both the Mental Development Index and the Psychomotor Index.[18-26] Most of these studies have involved small numbers of children, but two recent larger studies also showed lower developmental scores in infants with iron-deficiency anemia,[27, 28] although only one study[28] adequately controlled for sociodemographic confounders and neither controlled for lead exposure.

Thus the relative contributions of low-level lead exposure and iron deficiency to early childhood development remain to be clarified. This article describes a prospective study of lead exposure and iron status in children living in two towns in Kosovo, Yugoslavia. Because of the wide ranges of lead exposure and socioeconomic status, and the regular assessment of body iron stores, this study provided a unique opportunity to clarify these relationships during the first 2 years of life.

METHODS

Kosovska Mitrovica (K. Mitrovica), the site of a lead smelter, refinery, and battery plant, is an area of high lead exposure; Pristina, a town 25 miles to the south, has minimal lead exposure. Serbian and Albanian ethnic groups predominate in this region; a third ("other") group consists of Gypsies and other minorities. The study sample was derived from a prospective study of 1502 pregnant women living in those towns[29]; their pregnancy outcomes have been described previously.[30, 31] Of the 1502 women on whom data were obtained at mid pregnancy, complete data, including maternal and umbilical cord blood measures, were obtained at delivery from 1008 mother-infant pairs, 442 in K. Mitrovica and 566 in Pristina (Table I). The selection of infants for follow-up was restricted to those for whom complete delivery data were available. (The 494 infants for whom complete delivery data were not obtained were similar to the 1008 infants for whom complete delivery data were obtained with regard to maternal mid-pregnancy and delivery BPb levels,[31] age, smoking, and alcohol use. Their mothers did, however, have slightly less education and more prior births.) Further infant exclusion criteria included major central nervous system defects, chromosomal abnormalities, multiple births, and residence more than approximately 10 km from the pediatric clinic in either town.

Five groups of infants were selected for follow-up (Table I). In K. Mitrovica, mothers of 394 of the 418 eligible infants were asked to participate in the study; mothers of 24 eligible infants were not asked to participate because their infants' cord BPb concentrations were unavailable at the time of the quarterly matching, described below. The 394 infants were selected on the basis of their cord BPb concentrations: group 1, <15 μg/dl (n = 78); group 2, 15 to 20 μg/dl (n = 99); and group 3, >20 μg/dl (n = 217) (Table I). Nonexposed groups 4 and 5 were selected from eligible births in Pristina. Group 4 was selected to match group 1 in the distribution of umbilical cord BPb concentrations, to ensure that the cohort would include children with comparable prenatal lead exposure in both towns. Because births

Table II. Characteristics of study population at age 2 years

	Children not assessed	Children assessed		
		Total	K. Mitrovica	Pristina
No. of cases	314*	392	208	184
Birth weight (gm)	3272 ± 575†	3350 ± 499	3373 ± 514	3323 ± 480
Gender (% male)	53.2	51.9	52.4	51.4
Maternal education (yr)	9.9 ± 3.8‡	9.1 ± 3.9	8.9 ± 4.0	9.3 ± 3.8
Maternal age (yr)	26.5 ± 4.7	26.3 ± 4.9	26.1 ± 4.9	26.7 ± 4.8
Birth order	1.3 ± 1.4§	1.6 ± 1.7	1.5 ± 1.7	1.7 ± 1.7
Mid-pregnancy BPb (μg/dl)	13.3 ± 9.0	13.1 ± 9.2	19.9 ± 7.7	5.6 ± 2.0
Cord BPb (μg/dl)	15.5 ± 10.4	14.4 ± 10.4	22.2 ± 8.1	5.5 ± 3.3
Mid-pregnancy Hgb (gm/dl)	12.3 ± 1.1	12.4 ± 1.2	12.4 ± 1.1	12.3 ± 1.3
Cord Hgb (gm/dl)	16.3 ± 3.5	16.1 ± 2.5	15.8 ± 2.1	16.4 ± 3.0
Ethnicity (%)				
Albanian	52.8	57.5	53.6	62.0
Serbian	34.0‖	24.8	26.6	22.8
Other	13.2	17.7	19.8	15.2
Maternal IQ	33.8 ± 13.8	31.9 ± 12.7	32.9 ± 12.0	30.7 ± 13.3
(Raven raw score)	(*n* = 128)	(*n* = 382)		
HOME score	29.9 ± 7.2	29.0 ± 7.6	29.2 ± 7.2	28.7 ± 8.0
	(*n* = 121)	(*n* = 363)		
24-Month MDI	ND	105.2 ± 18.1	104.6 ± 18.5	105.8 ± 17.6

Values are expressed as mean ± SD.
IQ, Intelligence quotient; *ND*, not done.
*Consists of 185 cases in K. Mitrovica and 129 in Pristina.
†$p = 0.055$.
‡$p = 0.008$.
§$p = 0.014$.
‖$p = 0.020$.

of eligible infants occurred during a 20-month period and the first follow-up visit was to be at 6 months of age, this matching on the basis of BPb concentrations was done on a quarterly basis, that is, on the basis of data available from births during each 3-month interval. From the remaining births in Pristina during that quarter, group 5 was selected to match children in group 3 in the distribution of maternal and paternal education. This selection procedure was used to ensure that the Pristina cohort would include children with high and low cord BPb concentrations who were of comparable social class; a priori, the groups were not to be maintained in the statistical analysis, where greater power is obtained by considering the actual BPb levels.

Thus a total of 706 infants were invited to participate in a follow-up study involving serial visits made at 6, 12, 18, and 24 months of age. Of these, the parents of 541 infants consented and brought their infants to at least one visit. Of those who consented, 392 infants (72.5%) were examined at 24 months of age. The results of those 392 examinations are reported below.

At mid pregnancy, delivery, and each postnatal follow-up visit, venous blood samples were taken for the measurement of BPb,[32] erythrocyte protoporphyrin,[33] hemoglobin, and serum ferritin.[34] Blood specimens were refrigerated until transported to Columbia University, New York, N.Y., where the laboratory participates in the BPb and EP quality control program of the Centers for Disease Control, Atlanta, Ga. During this study, agreements with the quality control values for BPb and EP, measured by intraclass correlation coefficients, were 0.98 and 0.99, respectively. At each visit, weight, height, and head circumference were recorded; mothers were interviewed to obtain data concerning child and family health, diet, and demographic characteristics.

Cognitive development was assessed with the Mental scale of the Bayley Scales of Infant Development,[35] which has been used in Yugoslavia for more than a decade. The test was administered at ages 6, 12, 18, and 24 months by one of three Yugoslav psychologists. (In addition, the Psychomotor Scale was administered at ages 6 and 12 months). During frequent training and reliability visits by one of the authors (G.W.) with extensive experience with the Bayley Scales, tests were conducted by the Yugoslav staff, with independent scoring by the three psychologists and Dr. G. Wasserman. On 119 tests spanning the entire study period, the average intraclass correlation between Dr. Wasserman and the psychologists was 0.97. Furthermore, the addition of "tester" to the regression model, described below, did not

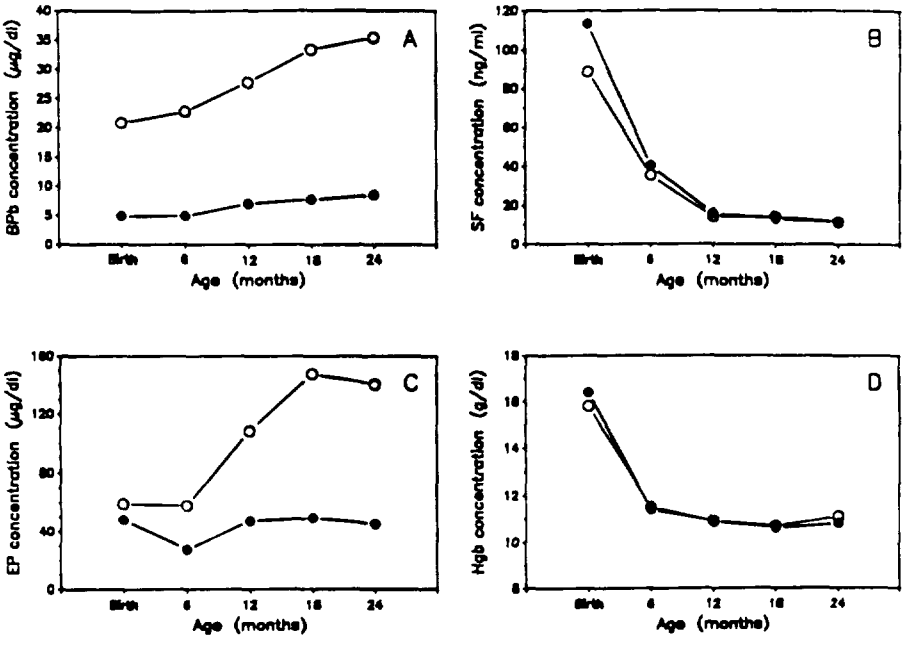

Fig. 1. Hematologic findings for children in K. Mitrovica *(clear circles)* and Pristina *(dark circles)* who were assessed at 24 months of age. A, Geometric mean BPb concentrations. B, Geometric mean serum ferritin concentrations. C, Geometric mean EP concentrations. D, Arithmetic mean hemoglobin concentrations. *SF*, Serum ferritin; *Hgb*, hemoglobin.

explain a significant amount of the variance. Thus reliability across testers was excellent.

The quality of the child-rearing environment was measured between 3 and 4 years of age by using an adaptation of the preschool version of the Home Observation for Measurement of the Environment,[36] which measures adult responsiveness to the child's requests and the types of stimulation available to the child. There is considerable stability in the HOME findings across age levels. One large study reported a correlation of 0.73[37] between 2 and 3 years of age; as a measure of reliability, this correlation indicates that 73% of the variance of each measure is shared with an underlying environmental factor.[38] The HOME scale was administered during a visit to the home by using a revised structured interview format (in Serbo-Croatian or Albanian) to increase reliability in the field. In addition, at the 24-month visit, mothers' intelligence was assessed by using Raven's Standard Progressive Matrices,[39] a nonverbal test relatively free of cultural influences.

Statistical analyses. Ordinary least-squares regression analysis was used to estimate associations between BPb, EP, serum ferritin, and hemoglobin concentrations, and the 24-month MDI. The regression models included a set of potentially confounding variables and covariates that are referred to as the core model. These variables were included to make our analyses comparable to reports from other studies, and to ensure that observed associations involving the MDI were not due to extraneous factors. The variables in the core model are themselves of secondary interest except to demonstrate that the social and demographic correlates of the MDI in our sample were similar to those observed in other settings. The variables in the core model are gender, birth order (first, second, third, or later), birth weight, ethnic group (Serbian, Albanian, other), HOME score, years of maternal education, maternal age, and maternal intelligence. Paternal education, which is strongly associated with maternal education, did not alter the associations among BPb levels, hemoglobin levels and MDI, and was excluded from the core variable set. In addition, we examined associations between the MDI and the study group by using indicator variables. Results were consistent with those reported here.

Exposure to lead was measured at five time points, and these measurements were strongly correlated. Three approaches were used to characterize exposure in the analyses. The first approach utilized BPb concentrations measured at the five individual time points to determine whether each individual measurement predicted the 24-month MDI. The second approach defined cumulative exposure as the area under the curve relating BPb concentration to age. The final approach defined incremental exposure as a series of difference scores between sequential BPb measurements.

Although hemoglobin level was a potential confounding variable in the analyses testing associations between BPb

Table III. Core model for 24-month MDI*

Variable	Coefficient	SE	p	R^2,† (%)
Ethnic Group				5.2
Serbian	9.480	2.715	0.0005	
Albanian	−0.820	2.265	0.7174	
Other	Reference			
HOME score	0.575	0.130	0.0001	3.8
Birth order				2.9
First	7.023	2.130	0.0011	
Second	Reference			
Third or greater	−1.015	2.216	0.6473	
Birth weight‡ (gm)	0.0055	0.0017	0.0011	2.1
Gender				2.1
Boy	−5.383	1.625	0.0010	
Girl	Reference			
Maternal intelligence (Raven raw score)	0.148	0.077	0.0567	0.7
Maternal education (yr)	0.348	0.278	0.2102	0.3
Maternal age‡ (yr)	0.159	0.191	0.4073	0.1
Intercept	80.40	—	—	—

*R^2 = 34.0%; n = 350.
†The change in R^2 represents the proportion of variance accounted for by each variable, after control for the others. Each R^2 was calculated as the difference in total R^2, including and excluding the particular variable from the full core model.
‡These variables were centered around their means to make their intercepts interpretable.

Table IV. Estimated change in 24-month MDI as BPb concentration increases from 10 to 30 μg/dl at blood sampling time points

Time of BPb measure	Estimated change (MDI points)*	Regression coefficient†	SEM‡	R^2,§ (%)	p
At birth (cord blood)	−1.66	−3.487	2.262	0.5	0.1242
At 6 mo	−1.13	−2.373	2.489	0.2	0.3412
At 12 mo	−1.74	−3.655	2.654	0.5	0.1697
At 18 mo	−1.77	−3.719	2.665	0.5	0.1640
At 24 mo	−2.53	−5.307	2.436	1.0	0.0301

*Estimated from five separate regression models (one per time point), each of which included the variables in the core model (Table II) and the appropriate concomitant log(BPb) and hemoglobin measures. The outcome is always 24-month MDI.
†Regression coefficient for log(BPb).
‡Standard error of the regression coefficient.
§The change in R^2 represents the proportion of variance accounted for by each BPb measure, after control for variables in the core model (Table III), as well as for the concurrent hemoglobin concentration.

Table V. Estimated change in 24-month MDI as hemoglobin decreases by 2 gm/dl at blood sampling time points

Time of hemoglobin measure	Estimated change (MDI points)*	Regression coefficient†	SEM‡	R^2,§ (%)	p
At birth (cord blood)	0.39	−0.195	0.311	0.1	0.5306
At 6 mo	2.74	−1.371	0.868	0.6	0.1153
At 12 mo	−2.62	1.312	0.805	0.6	0.1046
At 18 mo	−3.36	1.681	0.692	1.5	0.0158
At 24 mo	−1.71	0.857	0.587	0.5	0.1456

*Estimated from five separate regression models (one per time point), each of which included the variables in the core model (Table II) and the appropriate concomitant log(BPb) and hemoglobin measures. The outcome is always 24-month MDI.
†Regression coefficient for hemoglobin level.
‡Standard error of the regression coefficient.
§The change in R^2 represents the proportion of variance accounted for by each hemoglobin measure, after control for variables in the core model (Table III), as well as for the concurrent BPb concentration.

level and MDI, both it and iron status, as assessed by EP and serum ferritin levels, were central variables of interest in this study. Because deficits in hemoglobin are usually indicative of iron deficiency in this age group, hemoglobin level was examined as the primary indicator of iron status; serum ferritin and EP levels were explored as secondary indicators by adding them to the core model described above, with and without BPb level and hemoglobin level in the model.

RESULTS

Gender, maternal age, maternal intelligence, HOME scores, and prenatal lead exposure (i.e., maternal mid-pregnancy and umbilical cord BPb concentrations) did not

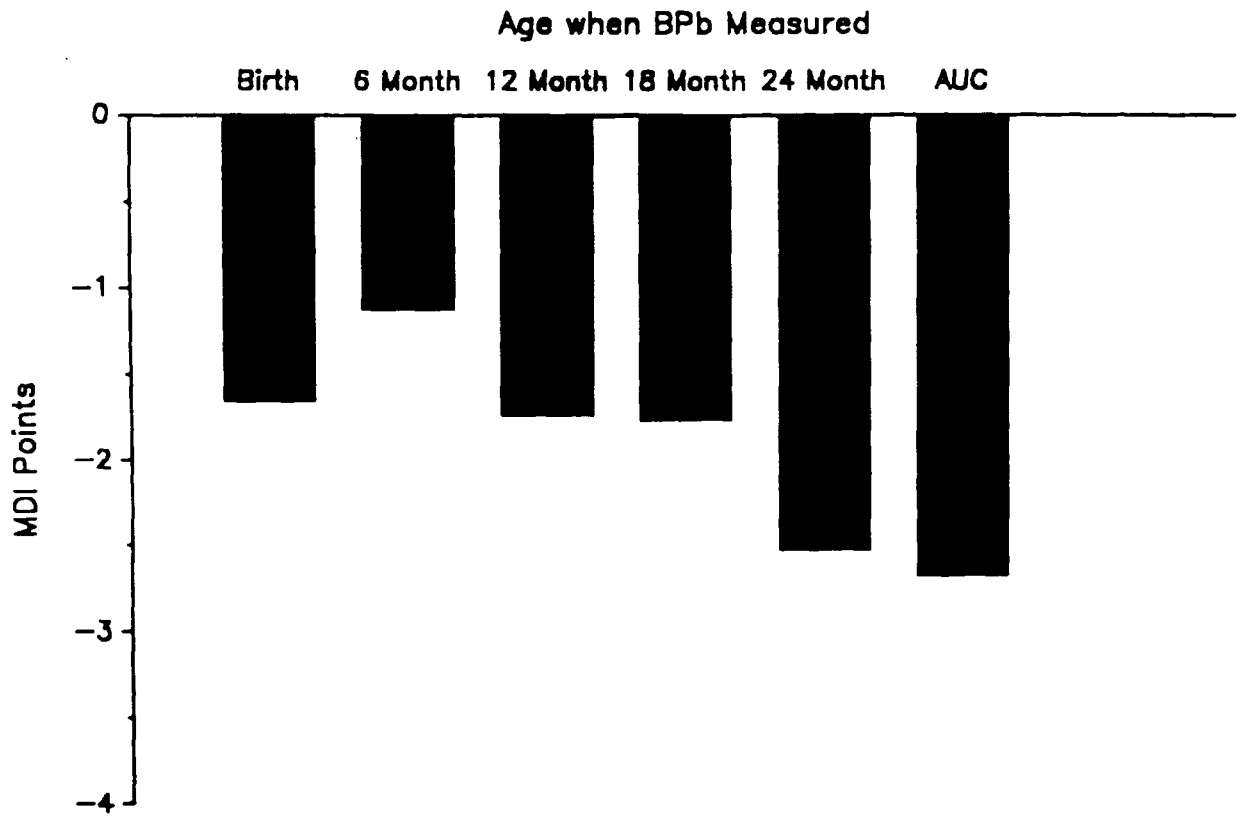

Fig. 2. Estimated change in 24-month MDI as BPb concentration increases from 10 to 30 μg/dl, after control for variables in core model (Table II), as well as for concurrent hemoglobin concentration. BPb concentration was log transformed. *AUC* represents the area under the curve for the plot of BPb concentration versus time; in effect, it represents the weighted average for BPb concentration.

differ between the 392 children assessed at 24 months of age and the 314 who were selected but not assessed (Table II). Small differences were found for several other characteristics. On average, those assessed were 75 gm heavier at birth ($p = 0.055$), were slightly less likely to be Serbian ($p = 0.02$), had mothers with approximately 1 year less education ($p = 0.008$), and were of slightly higher birth order ($p = 0.014$) than those not assessed.

Among those children assessed at 24 months of age, BPb concentrations were higher in K. Mitrovica than in Pristina. The geometric mean maternal mid-pregnancy BPb concentrations were 18.3 and 5.2 μg/dl, respectively ($p = 0.0001$). The cord BPb concentrations were 20.8 and 4.9 μg/dl, respectively ($p = 0.0001$). The groups of children assessed in the two towns did not differ significantly with regard to any characteristics other than BPb concentrations. The MDI scores at 2 years of age were comparable to U.S. norms. In contrast, maternal IQ and HOME scores were relatively low, perhaps reflecting the modest maternal education of this sample.

The geometric mean BPb concentrations of children in K. Mitrovica gradually rose from 20.8 μg/dl at birth to 35.4 μg/dl at 2 years of age; the largest increase occurred from 6 to 18 months of age. In Pristina it rose steadily from 4.9 to 8.5 μg/dl (Fig. 1, *A*). Geometric mean serum ferritin concentrations were essentially similar with time among children in the exposed and non-lead-exposed towns (Fig. 1, *B*). The EP concentrations, similar at birth, diverged beginning at 6 months of age (Fig. 1, *C*), suggesting that the higher EP concentrations observed in K. Mitrovica were due to differences in BPb concentrations rather than iron status. The hemoglobin values were similar with time in both towns (Fig. 1, *D*).

Before adjusting for potential confounders, we found no associations between any of the BPb measures and the MDI at 24 months of age. To examine the possibility that confounders may have masked an association, we examined associations adjusted for ethnicity, HOME score, birth order, birth weight, gender, maternal intelligence, maternal education, and maternal age. Relationships between these

variables and the MDI were similar to those observed in other settings. Ethnic group, likely a marker of socioeconomic status, accounted for the largest proportion of variance in the MDI (5.2%); the other variables are listed in Table III in order of their relative strengths of association with MDI. Increases in maternal education and intelligence were associated with increases in the children's MDI. Firstborn children scored higher than those of higher birth order, and children with better HOME scores did better than those from less stimulating homes. In addition, girls scored somewhat higher than boys.

Changes in the 24-month MDI attributable to each of the BPb and hemoglobin measures (from birth through 24 months) were examined by adding the concomitant BPb and hemoglobin concentrations at a given age to the core model. The consequences of a rise in BPb concentration from 10 to 30 μg/dl at each age, with control for the concurrent hemoglobin level, are depicted in Table IV. The decrement in IQ associated with BPb concentration was largest for the BPb concentration measured at 24 months, and accounted for 1.0% of the observed MDI variance. Nonsignificant deficits in the MDI were also associated with BPb concentrations measured from birth through 18 months. In addition, the lifetime exposure index (area under the curve) accounted for an incremental 0.9% of the variance, after the 24-month hemoglobin values and the core variables were taken into account (Fig. 2). The exclusion of maternal age and education from the regression model did not alter any of these findings (β for log 24-month BPb concentration = −5.64).

To examine the relative importance of prenatal versus postnatal lead exposure, we simultaneously included, in the model, cord BPb concentrations with a series of difference scores (i.e., changes in BPb concentrations between sequential visits). This analysis (data not shown) suggested that an increase in BPb concentration between 12 and 18 months of age was associated with the greatest decrement in the 24-month MDI ($p = 0.04$).

Iron deficiency anemia. When the children were 24 months of age, we observed a wide range of hemoglobin concentrations. In each town, deficits in hemoglobin appeared to be due primarily to iron deficiency. For example, among strata of children with increasing hemoglobin concentrations, serum ferritin concentrations were progressively higher whereas EP values were progressively lower (data not shown). In contrast, BPb concentrations did not systematically vary across hemoglobin strata. For example, among groups of 24-month-old children in K. Mitrovica with mean Hgb levels of <9.0, 9.0 to 9.9, 10.0 to 10.9, 11.0 to 11.9, 12.0 to 12.9, and ≥13.0 gm/dl, the mean BPb concentrations were 40.8, 39.8, 39.5, 36.7, 33.5, and 39.8 μg/dl, respectively. Thus, in each town, the observed cases of anemia were due primarily to iron deficiency, not to lead exposure.

Estimates of associations between hemoglobin level and MDI, with control for the concurrent BPb concentration, are presented in Table V. Unlike the pattern of results for the BPb exposure measures, the direction of the associations of hemoglobin level with MDI varied with age. Only at 12 months of age did decreased hemoglobin level begin to estimate a decrement in the 24-month MDI. The 18-month hemoglobin level was the only statistically significant predictor of 24-month MDI. A decline in hemoglobin level of 2 gm/dl at that age corresponded to an estimated decrease of 3.36 MDI points at 24 months of age (an incremental 1.46% of the MDI variance). None of the EP or serum ferritin measurements were associated with the 24-month MDI; the inclusion of BPb concentration, hemoglobin level, or both in the regression model did not alter this finding.

Low birth weight infants were not excluded from this study; the exclusion of 18 infants with birth weights <2500 gm from the statistical analyses presented above did not alter any of the reported findings. The statistical power of tests of interactions between hemoglobin and BPb concentrations was limited by sample size. Nonetheless, the addition of interactive terms at each time point were not statistically significant nor were they consistent in either direction or magnitude.

DISCUSSION

In this cohort of Yugoslav children, both prenatal and postnatal lead exposures were associated with small deficits in the 24-month MDI. In comparison with the combined contribution of social factors, the lead effect was very small, accounting at most for 1% of the variance. These results are generally consistent, in both direction and magnitude, with observations reported in several other ongoing prospective studies. For example, from a sample of primarily white, upper middle-class families, Bellinger et al.[7] selected infants for follow-up in three strata based on cord BPb concentration; group mean cord BPb concentrations were 1.8, 6.5, and 14.6 μg/dl, respectively. After adjustment for sociodemographic covariates, the cord BPb concentration was associated with small decrements in the MDI at 6, 12, 18, and 24 months of age.[7-9] Postnatal BPb concentration, however, was not associated with the MDI, perhaps because postnatal lead exposure was extraordinarily low.

A prospective study in Australia[13-15] involves primarily intact, white, middle-class families. Analyses relating lead exposure to 24-month MDIs suggested an adverse effect of prenatal and postnatal exposure.[15] The consequences of lead exposure became even more apparent by 48 months of age, at which time postnatal BPb concentrations were strongly associated with adjusted scores on the General

Cognitive Index of the McCarthy Scales of Children's Abilities.[13] At 4 years of age, the McCarthy General Cognitive Index decreased 7 points as the concurrent BPb concentration increased from 10 to 30 μg/dl.

A prospective study of predominantly African-American infants from single-parent families of low socioeconomic status in Cincinnati found that maternal prenatal and neonatal BPb concentrations (10 days of age) were related to MDI and Psychomotor Development Index (Bayley Scales) at 6 months of age.[10] More recently, however, this group reported that the 24-month MDI increased with increases in BPb concentration.[11] The inconsistency of the Cincinnati finding may relate to the social deprivation of that cohort; 85% of the mothers received public assistance, and the mean maternal IQ was 75. In the face of this social environment, it may be impossible to detect the consequences of lead exposure.

An additional study in Cleveland[12] followed a sample population of uniformly low socioeconomic status. By intent, half of this population were women with a history of alcoholism; mean maternal IQ was 74. At ages 24 and 36 months, cord BPb concentration was not associated with reduced developmental scores after consideration of covariates. It is not surprising that an adverse effect of lead exposure cannot be detected in the Cleveland cohort because of the combination of social deprivation and maternal alcohol use.

Fewer studies have tested the hypothesis that iron deficiency adversely affects early infant development.[18-28] In comparison with the prospective lead studies, these have often involved relatively small numbers of children and have often not made adjustment analytically for potential confounders. Associations between biochemical indexes of iron deficiency and the MDI are inconsistent,[20-22, 27] but positive associations between hemoglobin level and the Bayley MDI scores are reasonably consistent across studies.[18-28]

We also found an adverse association between anemia and the MDI, after adjustment for a number of variables including BPb level. Furthermore, the association was consistent in size in both towns, a finding that implicates an effect of anemia on the MDI that is independent of lead exposure. Moreover, a novel finding of this study relates to the observation that hemoglobin concentrations measured at 12 and 18 months of age, before the Bayley test at 2 years of age, were more strongly associated with the MDI than the hemoglobin concentration measured at the time of the test.

The serum ferritin level, an index of body iron stores, was not associated with the MDI, perhaps because ferritin concentrations asymptotically approach zero as iron deficiency develops. Because this and other studies have not found an association between biochemical indicators of iron status and MDI, we are unable to conclude with certainty that the observed association between hemoglobin level and MDI is solely due to iron deficiency. The majority (90.4%) of children in this study with hemoglobin concentrations ≤10.5 gm/dl had serum ferritin concentrations ≤12 ng/ml. Kosovo, Yugoslavia, is approximately 600 m above sea level and is not a region where hemoglobinopathies are prevalent. Only one of a sample of 200 women in the prospective study of pregnancy outcome had thalassemia minor; none was deficient in either folate or vitamin B_{12}. We therefore infer that the observed negative association between hemoglobin level and MDI is attributable to iron deficiency anemia.

On a global basis, because the prevalence of iron deficiency anemia in developing countries is high, its consequences for infant development may well exceed those of lead exposure. Nutritional intervention programs have been shown to be effective in preventing iron deficiency anemia in infants.[40] Our observation that the increment in BPb concentration between 12 and 18 months of age is associated with the lowest MDI at 2 years of age indicates that lead screening programs should aim to identify high-risk children by 12 months of age. We recommend that such programs also include screening for iron deficiency.

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